REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claims 1 and 16 are currently being amended and claims 41 and 42 are added. Upon entry of this amendment, claims 1, 3-12, 16-22, 29-31, 33-35 and 38-42 are presently pending in this application.

This amendment clarifies the properties of immortalized, epithelial tumor cells with metastatic potential of claims 1 and 16. Claims 41 and 42 are supported in pending claims 11 and 12. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

Applicants acknowledge the Examiner's withdrawal of all of the rejections under 35 U.S.C. 103 that were set forth in the previous Office Action dated November 22, 2002.

Rejections under 35 U.S.C. §112, first paragraph

Claims 1, 3-12, 16-22, 29-31, 33-35 and 38-40

Claims 1, 3-12, 16-22, 29-31, 33-35 and 38-40 (all of the pending claims) are rejected as allegedly failing to comply with the written description requirement because the Examiner alleges that newly amended claims 1 and 16 recite language that the Examiner contends is not described in the specification. Specifically, the Examiner states that the language "...wherein said cell was disseminated from a primary tumor, has the phenotype of the primary tumor" in claim 1, and "wherein...non-immortalized cell was disseminated from a primary tumor, has the phenotype of the primary tumor,..." in claim 16 does not support the language that the claimed cell has the same phenotype as the primary tumor.

Applicants have considered the Examiner's comments which form the basis of this rejection, and while not acquiescing to this rejection, and in an effort to expedite the long prosecution of this application, applicants have amended claims 1 and 16 to delete the

language "as the phenotype of the primary tumor." However, in response to the Examiner's comments, applicants submit that there is no contradiction in the in the present application because the "sameness" of the phenotypes is in respect to the immortalized tumor cell and its parental residual tumor cell. A fair reading of page 2, lines 31-34, informs the reader that there is a different expression of surface markers between the primary tumor cells and the epithelial tumor cells with metastatic potential. Whereas page 4, lines 28-32 compare the phenotype of the claimed immortalized, epithelial tumor cell with metastatic potential with the "residual tumor cells" present in the patient. Thus, it is not the phenotype of the primary tumor cell but the phenotype of the residual tumor cell present in the patient, which is considered to be conserved in the immortalized, epithelial tumor cell. Applicants submit that contrary to the Examiner's comments, these two portions of the specification do not disclose contradictory information.

The Examiner is referred to Example 7 of the present application, which provides an experiment on the phenotypic analysis of the epithelial differentiation antigen in the immortalized tumor cells. This example provides a detailed phenotypic analysis of epithelial differentiation antigens in the expanded CK+ cells as summarized in Table 3. Specifically, on page 27, lines 7-10, the specification recites that the results of this phenotypic analysis suggests "...that the integration of the SV40 DNA and expression of the large T antigen did not substantially change the expression pattern of the studied differentiation markers." Additionally, on page 28, lines 7-12, the specification recites that "the method established here appears to be a feasible way to generate large quantities of cells that are derived from the earliest metastasizing cells and that apparently have conserved the phenotype of the residual tumor cells present in the patient."

In view of these arguments and a clarification amendment to claims 1 and 16, it is requested that this rejection be withdrawn in regard to the rejected claims.

Claim 35

Claims 35 is rejected as allegedly failing to comply with the enablement requirement. The Examiner states that claim 35 reads on the treatment of numerous epithelially derived

tumors with a therapeutically effective amount of an immortalized epithelial tumor cell. The Examiner states that the present specification does not provide evidence of the use of an immortalized epithelial tumor cell for treating any neoplasms *in vivo* or data that supports the administration of immortalized epithelial tumor cell.

Applicants respectfully traverse this rejection and refer the Examiner to Examples 6 and 8 of the present specification in support of the enablement of claim 35.

Example 6 provides an example in which the claimed immortalized epithelial cells of the present invention is introduced into SCID mice and local tumor growth and micrometastatic bone marrow infiltration was observed.. These results show that micrometastatic cells propagated from bone marrow aspirates maintain a particular organ-specific homing affinity in SCID-mice. These animals provide a model for studying the *in vivo* immune response against minimal residual cancer when autologous immune effector cells are introduced. This animal model is useful for testing genetically engineered tumor cell vaccines directed against minimal residual cancer.

Example 8 provides an example of the *in vitro* generation of an autologous T cell response to micrometastatic carcinoma cells propagated from bone marrow of a prostate cancer patient who did not exhibit overt metastasis (stage M_0). These cells were transduced with a gene encoding the co-stimulatory molecule B7. The results show that autologous PBLs which were repeatedly stimulated *in vitro* on an irradiated monolayer of B7 transfected tumor cells consisting of 75%-85% $CD3^+CD8^+$ T-cells. These cells lysed 15% to 20% B7-transfected cells (PC-MM-1). This study suggests to a person skilled in the art that transduced B7 micrometastatic tumor cells would be useful in enhancing the cellular immune response against these tumor cells and that these cells can be used to generate large quantities of specific cytotoxic effector cells from patient's blood samples.

In regard to the *Wands* factors, applicants submit that one skilled in the art would be able to extrapolate from the SCID mouse and generation of autologous T cell experiments to support a method of therapy claims in the present invention. As provided in Examples 6 and 8, a skilled person can inject a bone marrow sample containing suspected micrometastatic

tumor cells to determine if they still carry the phenotype necessary to cause a tumor in the SCID mice or to stimulate autologous T-cells to make them $CD3^{+}CD8^{+}$. Applicants submit that the examples provide guidance to the skilled person to select appropriate epithelial tumor cells without metastatic potential which is then transduced with an immortalizing oncogene and expanded in numbers. The method of treatment utilizes these cells to treat a patient and the patient is monitored to assess the state of the patient's cancer. Applicants submit that treating a patient with the cells, as defined in claims 1, 41 or 42, does not require undue experimentation, and applicants request the withdrawal of this rejection in view of the guidance provided in the specification and the skill of those scientists and medical person in the field of oncology and immunology.

41 1642

Atty. Dkt. No. 028622-0101

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Achim Dickmanns et al.

Title: IMMORTALIZED EPITHELIAL TUMOR CELLS

Appl. No.: 08/981,583

Filing Date: 02/03/1998

Examiner: Alana M. Harris

Art Unit: 1642

AMENDMENT TRANSMITTAL

Commissioner for Patents
PO Box 1450
Alexandria, Virginia 22313-1450

Sir:

Transmitted herewith is an amendment in the above-identified application.

[X] Small Entity status under 37 C.F.R. § 1.9 and § 1.27 has been established by a previous assertion of Small Entity status.

[ ] Assertion of Small Entity status is enclosed.

[X] The fee required for additional claims is calculated below:

	Claims As Amended		Previously Paid For		Extra Claims Present		Rate		Additional Claims Fee
Total Claims:	29	□	31	=	0	x	$18.00	=	$0.00
Independents:	2	□	3	=	0	x	$86.00	=	$0.00
First presentation of any Multiple Dependent Claims:						+	$290.00	=	$0.00
					CLAIMS FEE TOTAL:			=	$0.00

10/23/2003 EAREGAY1 00000024 08981583
01 FC:2251 55.00 OP